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A Prospective, Multicenter, Randomized Trial to Assess Efficacy of Pioglitazone on In-Stent Neointimal Suppression in Type 2 Diabetes

POPPS (Prevention of In-Stent Neointimal Proliferation by Pioglitazone Study)

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Objectives The aim of this study was to clarify whether pioglitazone suppresses in-stent neointimal proliferation and reduces restenosis and target lesion revascularization (TLR) after percutaneous coronary intervention (PCI).

Background Previous single-center studies have demonstrated the anti-restenotic effect of a peroxisome proliferator-activated receptor gamma agonist, pioglitazone, after PCI.

Methods A total of 97 patients with type 2 diabetes mellitus (T2DM) undergoing PCI (bare-metal stents only) were enrolled. After PCI, patients were randomly assigned to either the pioglitazone group (n = 48) or the control group (n = 49). Angiographical and intravascular ultrasound (IVUS) imaging were performed at baseline and repeated at 6-month follow-up. Primary end points included angiographical restenosis and TLR at 6 months follow-up. Secondary end point was in-stent neointimal volume by IVUS.

Results Baseline glucose level and glycosylated hemoglobin (HbA1c) level were similar between the pioglitazone group and the control group. Angiographical restenosis rate was 17% in the pioglitazone group and 35% in control group (p = 0.06). The TLR was significantly lower in pioglitazone group than in control group (12.5% vs. 29.8%, p = 0.04). By IVUS (n = 56), in-stent neointimal volume at 6 months showed a trend toward smaller in the pioglitazone group than in the control group (48.0 ± 30.2 mm^3 vs. 62.7 ± 29.0 mm^3, p = 0.07). Neointimal index (neointimal volume/stent volume × 100) was significantly smaller in the pioglitazone group than in the control group (31.1 ± 14.3% vs. 40.5 ± 12.9%, p = 0.01).

Conclusions Pioglitazone treatment might suppress in-stent neointimal proliferation and reduce incidence of TLR after PCI in patients with T2DM. (J Am Coll Cardiol Intv 2009;2:524–31)

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Since the introduction of the drug-eluting stent (DES), incidence of in-stent restenosis (ISR) decreased dramatically and consistently compared with bare-metal stent (BMS) (1,2). Despite the aggressive use of DES, ISR still occurs in some high-risk patients.

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Previous studies have demonstrated that diabetes is 1 of the strongest clinical predictors of ISR after DES (3–6) as well as BMS (7,8). More important, diabetes is also an independent predictor of stent thrombosis. Recent concerns about very late stent thrombosis have raised questions about the unselected use of DES to treat patients with high likelihood of recurrent luminal narrowing after percutaneous coronary intervention (PCI) (9,10).

Pioglitazone, 1 of the thiazolidinediones (TZDs) used to treat type 2 diabetes mellitus (T2DM), has been shown to reduce neointimal proliferation after BMS placement (11). Although single-center studies have shown possible inhibitory effects of in-stent neointimal proliferation by TZDs (11–16), the impact of neointimal inhibition on clinical end points has not been confirmed by any multicenter study (11,17).

Accordingly, we hypothesized that pioglitazone treatment might suppress in-stent neointimal proliferation and decrease incidence of restenosis and target lesion revascularization (TLR).

Methods

Study design. The POPPS study (prevention of in-stent neointimal proliferation by pioglitazone study) is a prospective, multicenter, open-label, randomized, controlled study to investigate efficacy of pioglitazone on neointimal suppression after PCI in patients with T2DM and symptomatic ischemic heart disease.

Between July 2003 and March 2006, patients with both T2DM and symptomatic ischemic heart disease (stable angina pectoris, unstable angina pectoris/non–ST-segment elevation myocardial infarction (MI), or ST-segment elevation MI) who underwent PCI were enrolled in this study. Patients were diagnosed as T2DM if: 1) fasting plasma glucose level was >126 mg/dl; 2) glucose level 2 h after 75-g oral glucose tolerance test was ≥200 mg/dl; or 3) patient had a known medical history of T2DM. Exclusion criteria were presence of end stage disease, cardiogenic shock or congestive heart failure at the time of PCI, contraindication to antiplatelet therapy, patients who were already taking pioglitazone, patients with gastrointestinal bleeding or transient ischemic attack, ineligible for coronary artery bypass grafting, and ineligible for PCI.

After PCI, patients were randomly assigned to either the pioglitazone (30 mg daily) or the control group. On average, pioglitazone was started 3 days after the PCI procedure. Any antidiabetic medications other than TZDs were allowed in either the pioglitazone or the control group to optimally control diabetic status.

Angiographic and intravascular ultrasound procedure. Coronary angiography was performed following the standard femoral or radial approach. All patients received intravenous heparin (100 U/kg) before the procedures. After intracoronary nitroglycerin (200 μg) or isosorbide dinitrate (2 mg) administration, diagnostic angiography was performed. Intravascular ultrasound (IVUS) imaging was performed at baseline and repeated after PCI. Because DES was not available at the time of the initial enrolment, DES was not allowed throughout the entire study period. Intravascular ultrasound imaging was performed with automated pullback device at a rate of 0.5 mm/s.

After diagnostic IVUS examination, PCI was performed in a usual manner to achieve diameter stenosis of <25% with Thrombolysis In Myocardial Infarction flow grade 3. After PCI, patients were maintained on a regimen of aspirin (81 to 100 mg daily) plus ticlopidine (200 mg daily) for at least 4 weeks. Cilostazole (200 mg daily) was alternatively used, if ticlopidine was not tolerable. In this study period, either clopidogrel or glycoprotein IIb/IIIa inhibitors were not available.

Quantitative coronary angiography. All angiography was analyzed at an independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, California) by an analyst (K.W.) blinded to the clinical and IVUS information. Angiographic frames were digitized and analyzed with an automated edge-detection algorithm (Quant32, Sanders Data Systems, Palo Alto, California). The minimal lumen diameter (MLD) inside and outside the stent and reference diameter were used to calculate the percent diameter stenosis before and after PCI.

Ultrasound imaging protocol. A commercially available system (CVIS/Boston Scientific Corporation, San Jose, California) was used for IVUS examination. The system consisted of a single-element 40-MHz transducer mounted on the tip of a flexible shaft and rotating at 1,800 rpm within a 2.6-F rapid exchange/common distal lumen imaging sheath. Ultrasound images were recorded on half-inch, Super-VHS videotape for offline quantitative analysis.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CSA = cross-sectional area
DES = drug-eluting stent(s)
EEM = external elastic membrane
HbA1c = glycosylated hemoglobin
ISR = in-stent restenosis
IVUS = intravascular ultrasound
MI = myocardial infarction
MLD = minimal lumen diameter
PCI = percutaneous coronary intervention
P+M = plaque plus media
TLR = target lesion revascularization
TZDs = thiazolidinediones
T2DM = type 2 diabetes mellitus

Quantitative and qualitative coronary ultrasound analysis. All ultrasound images were reviewed and evaluated for both qualitative and quantitative parameters at an independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University) by an analyst (M.Y.). The images were digitized to perform morphometric analysis with commercially available planimetry software (echoPlaque, Indec Medical Systems, Santa Clara, California). Lumen and stent cross-sectional areas (CSA) were measured throughout the stented segment at 1.0-mm increments. Neointimal CSA was then calculated as a difference between stent and lumen CSA. Lumen, stent, and neointimal volume were calculated with Simpson's method. Neointimal index was calculated as: neointimal volume/stent volume × 100 (18). Lumen and external elastic membrane (EEM) CSA were measured at 1.0-mm increments for 5.0 mm from both proximal and distal stent edges in a subset of patients. Plaque plus media (P+M) CSA was calculated as EEM minus lumen CSA. The EEM, lumen, and P+M volume were calculated with Simpson's method. The EEM, lumen, and P+M volume index were calculated as volumes divided by 5 mm.

Clinical follow-up. Thirty-day clinical events, including death, MI, TLR, and heart failure, were documented by chart review.

Long-term clinical events, including death, MI, TLR, heart failure requiring hospital stay, and peripheral edema requiring diuretics, were also obtained both at 6 and 12 months after the index PCI procedure. Target lesion revascularization was defined as clinically driven repeat revascularization (either repeat PCI or coronary artery bypass grafting) of the initially treated target lesion, including stented segments and peri-stent segments 5 mm from both proximal and distal stent edges.

Study end points. Primary end points of this study were angiographical restenosis rate and TLR rate at 6 months.

Secondary end point was in-stent neointimal volume or neointimal index by IVUS.

Statistical analysis. With a 2-sided test for differences in independent binomial proportions with an alpha level of 0.05, we calculated that 95 patients would have to undergo randomization for the study to have 80% power to detect a reduction in the primary end point of ISR from an anticipated 43% in the control group to 17% in the pioglitazone group. Quantitative data were presented as a mean ± SD or median with interquartile range, depending on the distribution of the variable, and qualitative data were presented as frequencies. Continuous variables were compared with paired and unpaired *t* tests. If normality failed, Wilcoxon test and Mann-Whitney test were used. Binary variables were examined by use of Fisher exact and chi-square tests. All p values are 2-sided and not adjusted for multiplicity. All statistical analyses were performed with the Statview version 5.0 (SAS Institute, Cary, North Carolina).

Results

Clinical characteristics. A total of 97 patients were enrolled in this study. There were 82 men and 15 women, with a mean age of 63 ± 9 years. Among all patients, 26 (27%) had stable angina pectoris, 22 (23%) had unstable angina pectoris/non-ST-segment elevation MI, and 49 (51%) had ST-segment elevation MI.

After randomization, 48 patients were assigned to the pioglitazone group and 49 patients to the control group. Baseline clinical characteristics were well-matched, with no significant differences in the frequency of the clinical risk factors (Table 1). Lesion characteristics were also well-matched between the 2 groups (Table 2).

Procedure characteristics. There were no significant differences in interventional procedures (Table 2). Mean stent size was 3.5 mm in both groups, and maximal balloon inflation pressure was 13.5 atm in the pioglitazone group versus 13.9 atm in the control group (p = NS).

Laboratory data and medications. Laboratory data at baseline and at follow-up are summarized in Table 3. Fasting glucose and glycosylated hemoglobin (HbA1c) levels were similar between the groups at baseline and at 6-month follow-up. During 6-month follow-up, fasting glucose and HbA1c level significantly decreased in both groups. Similarly, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride level did not differ between the groups either at baseline or at follow-up. C-reactive protein did not differ either at baseline or at follow-up between the 2 groups. Serial change (Delta) in each laboratory data was calculated as each value at follow-up minus that at baseline. Delta fasting glucose, Delta HbA1c, Delta total cholesterol, Delta low-density lipoprotein cholesterol, Delta high-density lipoprotein cholesterol, Delta triglyceride, and Delta C-reactive protein were similar between the 2 groups (all p = NS).

Medications other than pioglitazone are summarized in Table 4. There were no significant differences in medica-

Table 1. Clinical Characteristics

	Pioglitazone (n = 48)	Control (n = 49)	p Value
Age (yrs), mean ± SD	64.0 ± 8.8	62.4 ± 9.8	NS
Male, n (%)	40 (83)	42 (86)	NS
Risk factors, n (%)			
Hypertension	32 (67)	26 (53)	NS
Diabetes	48 (100)	49 (100)	—
Dyslipidemia	28 (58)	29 (59)	NS
Smoking	24 (50)	26 (53)	NS
Family history	6 (13)	6 (12)	NS
History of MI, n (%)	11 (23)	9 (18)	NS
CABG, n (%)	1 (2)	3 (6)	NS

CABG = coronary artery bypass grafting; MI = myocardial infarction.

Table 2. Procedural Characteristics

	Pioglitazone (n = 48)	Control (n = 49)	p Value
Clinical presentation			
SAP/UAP/AMI	14/10/24	12/12/25	NS
Target lesion			
LAD/LCX/RCA	17/8/23	22/14/13	NS
Lesion type			
A or B1/B2 or C	22/26	22/27	NS
Stent size, mm	3.5 ± 0.4	3.5 ± 0.5	NS
Stent length, mm	17.0 ± 4.5	17.5 ± 5.5	NS
Final balloon size, mm	3.5 ± 0.4	3.5 ± 0.5	NS
Maximal balloon inflation pressure, atm	13.5 ± 2.9	13.9 ± 3.1	NS

AMI = acute myocardial infarction; LAD = left anterior descending artery; LCX = left circumflex; RCA = right coronary artery; SAP = stable angina pectoris; UAP = unstable angina pectoris.

tions. Among all patients, statin was prescribed in 59% and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers were prescribed in 59%; insulin was used in 7%, sulfonylurea in 43%, alfa-glucosidase inhibitors in 23%, and metformin in 9%.

Quantitative coronary angiography results. Coronary angiography was repeated in 86 patients (46 in the pioglitazone group, 40 in the control group) at 6 months. Quantitative coronary angiography results are shown in Table 5. There were no significant differences in pre-intervention reference vessel size, MLD, pre-intervention percent diameter stenosis, and lesion length. Similarly, MLD and percent diameter stenosis after intervention did not differ between the 2 groups.

At 6-month follow-up, MLD showed a trend toward larger in the pioglitazone group than in the control group (p = 0.08) (Table 5). Percent diameter stenosis was significantly lower in the pioglitazone group. Late loss was significantly smaller in the pioglitazone group. The frequency of binary restenosis was 17% in the pioglitazone group and 35% in the control group (p = 0.06) (Fig. 1).

Table 4. Medications

	Pioglitazone (n = 48)	Control (n = 49)	p Value
Aspirin	48 (100)	49 (100)	NS
Ticlopidine	40 (83)	40 (82)	NS
Cilostazole	8 (17)	9 (18)	NS
Nitrates	16 (33)	17 (35)	NS
Nicorandil	17 (35)	15 (31)	NS
Calcium antagonists	12 (25)	11 (22)	NS
Beta-blockers	18 (38)	19 (39)	NS
ACEI	18 (38)	11 (22)	NS
ARB	13 (27)	15 (31)	NS
Diuretics	5 (10)	10 (20)	NS
Statin	31 (65)	26 (53)	NS
Insulin	2 (4)	5 (10)	NS
Sulfonylurea	20 (42)	22 (45)	NS
Alfa-GI	8 (17)	14 (29)	NS
Metformin	3 (6)	6 (12)	NS

Values are n (%).
ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; Alfa-GI = alpha-glucosidase inhibitors.

IVUS results. IVUS imaging was performed in 56 patients (28 in each group) at 6 months. In-stent neointimal volume at 6-month follow-up was 48.0 ± 30.2 mm^3 in the pioglitazone group and 62.7 ± 29.0 mm^3 in the control group (p = 0.07). Neointimal index was significantly smaller in the pioglitazone group than in the control group (31.1 ± 14.3% vs. 40.5 ± 12.9%, p = 0.01) (Fig. 1).

Stent edge measurements were available in 42 edges from 29 patients (14 in the pioglitazone group and 15 in the control group). Serial changes in EEM, P+M, and lumen volume index did not differ between the pioglitazone group and the control group (Fig. 2).

30-day and long-term clinical follow-up. The 30-day clinical events including death (0% vs. 0%), MI (2.0% vs. 2.0%), and TLR (2.0% vs. 0%) were similar between the pioglitazone group and the control group. Congestive heart failure was not documented during the initial hospital stay.

Table 3. Laboratory Data

	Pioglitazone (n = 48)		Control (n = 49)		
	Baseline	Follow-Up	Baseline	Follow-Up	p Value
Fasting glucose, mg/dl	170 ± 73	132 ± 45*	162 ± 63	145 ± 55*	NS
HbA1c, %	7.5 ± 1.8	6.8 ± 1.0*	7.0 ± 1.5	6.5 ± 1.2*	NS
Total cholesterol, mg/dl	197 ± 48	188 ± 27	202 ± 39	184 ± 39*	NS
LDL cholesterol, mg/dl	119 ± 39	111 ± 28	124 ± 30	107 ± 31*	NS
HDL cholesterol, mg/dl	44 ± 15	49 ± 12*	44 ± 10	48 ± 18	NS
Triglyceride, median (IQR), mg/dl	139.5 (90.0–209.0)	129.5 (99.0–172.0)	145.0 (102.0–209.0)	123.5 (91.0–170.0)	NS
CRP, median (IQR), mg/l	3.0 (1.2–4.0)	1.1 (0.6–3.9)	2.0 (1.0–7.5)	1.3 (0.48–3.3)	NS

*p < 0.05 versus baseline.
CRP = C-reactive protein; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

Table 5. Quantitative Coronary Angiography

	Pioglitazone (n = 46)	Control (n = 40)	p Value
Before			
Reference diameter, mm	2.55 ± 0.48	2.47 ± 0.56	NS
MLD, mm	0.65 ± 0.56	0.66 ± 0.52	NS
Diameter stenosis, %	75.2 ± 20.4	73.3 ± 20.8	NS
Lesion length, mm	10.5 ± 5.0	10.4 ± 5.5	NS
After			
MLD, mm	2.54 ± 0.43	2.54 ± 0.47	NS
Diameter stenosis, %	6.8 ± 13.6	6.1 ± 11.2	NS
Follow-up			
MLD, mm	1.83 ± 0.56	1.57 ± 0.65	0.08
Diameter stenosis, %	26.2 ± 16.6	36.0 ± 23.1	0.03
Binary restenosis rate, %	17.4	35.0	0.06
Late loss, mm	0.69 ± 0.52	1.00 ± 0.49	0.02

MLD = minimal lumen diameter.

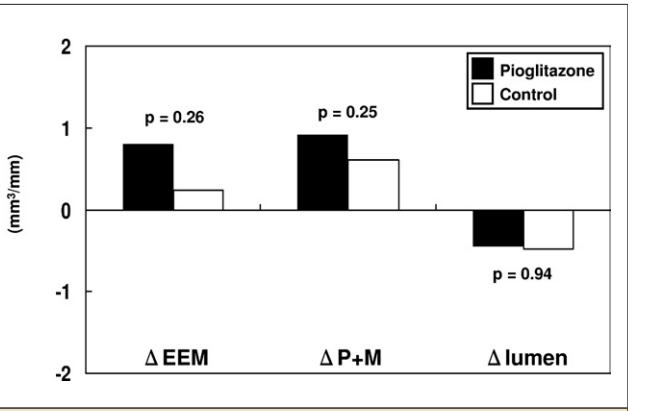

Figure 2. Serial Changes in Intravascular Ultrasound Parameters at Stent Edges During 6-Month Follow-Up

ΔEEM = serial changes in external elastic membrane volume index; ΔP+M = serial changes in plaque plus media volume index; Δlumen = serial changes in lumen volume index.

Long-term clinical follow-up at 6 months are summarized in Table 6. Incidence of death and MI did not differ between the 2 groups. In contrast, TLR (all repeat PCI) rate was significantly lower in the pioglitazone group than in the control group (12.5% vs. 29.8%, p = 0.04) (Fig. 1). As a result, the major adverse cardiac event (death, MI, or TLR) rate was significantly lower in the pioglitazone group than the control group (13% vs. 31%, p = 0.02).

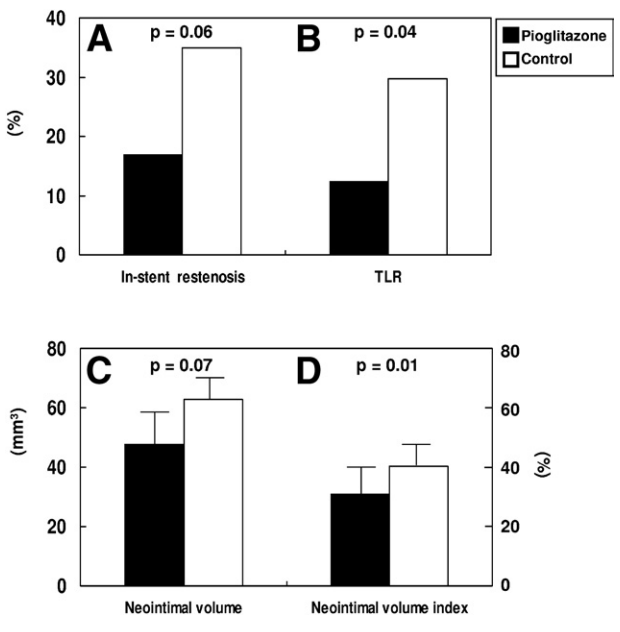

Figure 1. Primary and Secondary End Points

(A) Angiographic restenosis at 6 months after percutaneous coronary intervention with and without pioglitazone. Restenosis rate showed a trend toward lower in the pioglitazone group than in the control group. **(B)** Target lesion revascularization (TLR) at 6 months. The TLR rate was significantly lower in the pioglitazone group than in the control group. **(C)** In-stent neointimal volume and **(D)** neointimal volume index at 6 months. Neointimal volume index was significantly lower in the pioglitazone group than in the control group. **Open bars** represents pioglitazone group; **solid bars** represents control group.

Congestive heart failure requiring a hospital stay was similarly observed in both groups (2% vs. 4%, p = NS). Peripheral edema requiring diuretics tended to be more frequently observed in the pioglitazone group than in the control group (4% vs. 0%, p = NS), although the difference did not reach statistical significance.

At 12-month follow-up, death (2% vs. 6%, p = 0.29) and MI (2% vs. 2%, p = 0.99) were similar between the 2 groups. The TLR (12.5% vs. 31.9%, p = 0.02) as well as major adverse cardiac events (14.6% vs. 36.2%, p = 0.01) were significantly lower in the pioglitazone group than the control group.

Discussion

The main findings of this study were as follows: 1) pioglitazone reduced incidence of angiographical restenosis and

Table 6. Clinical Follow-Up at 6 Months

	Pioglitazone (n = 48)	Control (n = 47)	p Value
Death	0 (0)	0 (0)	NS
MI	1 (2)	1 (2)	NS
TLR	6 (13)	14 (29.8)	0.04
MACE	6 (13)	15 (32)	0.02
Congestive heart failure	1 (2)	2 (4)	NS
Peripheral edema	2 (4)	0 (0)	NS
Hypoglycemia	0 (0)	0 (0)	NS

Values are n (%).

MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization.

TLR after PCI without increasing incidence of death, MI, congestive heart failure, or peripheral edema; and 2) IVUS investigation revealed that pioglitazone significantly suppresses in-stent neointimal proliferation.

Our present results were in concordance with previous single-center studies (11–15,19). Takagi et al. (12) first reported that troglitazone significantly reduced ISR. Subsequently, Takagi et al. (11) demonstrated that pioglitazone similarly reduced in-stent neointimal volume by IVUS and possibly decreased incidence of ISR and TLR. However, the impact of pioglitazone on clinical end points did not reach statistical significance, possibly because of small sample size (11).

Efficacy of pioglitazone on neointimal suppression was also evaluated in patients without diabetes (20,21). Marx et al. (20) demonstrated similar neointimal inhibitory effect among a non-diabetic population. Similarly, Katayama et al. (21) demonstrated neointimal suppression of pioglitazone in non-diabetic patients with metabolic syndrome.

Although efficacy of TZDs on neointimal proliferation has been reported consistently and repeatedly, these data were limited by the single-center study design and a lack of an independent core laboratory for image analysis. Therefore, our present study was designed and conducted to overcome these limitations and clearly confirmed that pioglitazone significantly suppresses in-stent neointimal proliferation and, as a result, decreased the rate of in-stent restenosis and lowered the chance of TLR. Because glycemic control as well as lipid prolife did not differ between those treated with and without pioglitazone, it is unlikely that glycemic control itself affected neointimal suppression. Therefore, the pleiotropic effect of TZDs might be associated with neointimal suppression. There are several possible mechanisms by which pioglitazone affects in-stent neointimal proliferation. First, it has been reported that TZDs have an inhibitory effect on smooth muscle migration and proliferation in animal models (22–25). This might be related to less neointimal proliferation after vascular injury made by metallic stent implantation. Second, Aizawa et al. (26) reported that pioglitazone might enhance apoptosis in vascular smooth muscle cells. Third, anti-inflammatory effects of TZDs have been reported, possibly affecting the restenotic process (27–29). Although C-reactive protein level did not significantly change over time after pioglitazone administration in this study, a small but significant impact of TZDs on local inflammation might play a role. In fact, results from a recently published larger-scale randomized study demonstrated that pioglitazone more favorably affected C-reactive protein than glimepiride (30). Fourth, an antithrombotic effect of pioglitazone has been reported (31–33). Therefore, this might be related to suppression of an early vascular response (i.e., fibrin formation) after stent implantation that leads to subsequent neointimal proliferation and restenosis (34). Finally, pioglitazone has been reported to decrease fasting insulin level, because of its insulin sensitizing effect (30). Hyperinsulinemia is a known promoter of atherosclerosis progression and neointimal proliferation after intervention (18). Although fasting insulin level has not been evaluated, it is possible that decreased fasting insulin affected the results (30).

In our present study and some other previous studies (11,19), pioglitazone was initiated after PCI. In contrast, some investigators started pioglitazone before PCI (15,20). It is unknown whether pre-treatment has some advantage over post-treatment strategy to prevent restenosis. Further study is needed to compare pretreatment and post-treatment strategies to prevent ISR in T2DM patients. Also, it needs to be investigated how long pioglitazone should be continued to affect neointimal suppression.

Recently, pioglitazone has been reported to decrease the incidence of cardiovascular events in T2DM patients with a previous history of MI (35,36). This favorable effect might be explained by the antiatherosclerotic effect of this drug. The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) trial has demonstrated that pioglitazone treatment might suppress carotid intima-media thickness as compared with glimepiride (37). More recently, the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) trial has shown that pioglitazone treatment dramatically suppresses coronary atherosclerosis progression as compared with glimepiride (30). In our present study, we did not find significant differences in serial changes of atherosclerotic plaque between the pioglitazone and control group. This discordant result might be due to small sample size. Our study is not powered to investigate the impact of pioglitazone on untreated atherosclerotic segments. However, our present study further addresses the efficacy of pioglitazone on treated (stented) coronary vessel wall.

The impact of our results in the era of DES might be controversial. Diabetes is still the strongest independent clinical predictor of ISR and stent thrombosis after DES implantation (4,38–41). Therefore, it is possible that TZDs further decrease ISR even after DES implantation. The impact of TZDs on neointimal proliferation after DES implantation should be investigated. Furthermore, recent concerns about the small but significant increased risk for very late stent thrombosis raised a question about unselected or universal use of DES, and thus it is recommended that DES should be used only for patients who tolerate extended (>12 months) dual antiplatelet therapy (42–44). Pioglitazone might be adjunctively used to decrease the chance of ISR in high-risk patients for ISR after BMS treatment in the era of DES.

Several publications have suggested possible unfavorable effects of TZDs that increase incidence of MI and heart failure (45,46). A meta-analysis by Nissen and Wolski (45)

demonstrated that rosiglitazone treatment potentially increased the incidence of MI, although another meta-analysis and report from a large-scale randomized trial did not conclude this unfavorable effect (47). However, a large-scale randomized study as well as a meta-analysis of the randomized trials did not show increased risk of MI but rather demonstrated decreased incidence of MI or death after pioglitazone treatment (35,48). In our present study, 2 cases were reported to have MI during follow-up, 1 in each group. One case in the pioglitazone group had an MI associated with subacute stent thrombosis. Another case in the control group had a periprocedural MI. Therefore, it is unlikely that either is related to any anti-diabetic medications. It is well-known that TZDs increased small but significant numbers of peripheral edema and congestive heart failure (49). In our present study, despite a high-risk clinical profile, peripheral edema and congestive heart failure did not statistically increase.

Study limitations. Our study has some limitations. First, although pioglitazone might be efficacious in some patients with T2DM, incidence of ISR is still higher than in those patients who are treated with DES. Second, although a favorable effect of pioglitazone on long-term clinical outcome has been reported by a large-scale randomized trial, our present study is not powered to address the long-term prognostic impact of pioglitazone. Therefore, the longer-term clinical impact of pioglitazone will be required to address this issue. Third, because our study has multiple end points without adjustment for multiplicity, the possibility of type 1 error could not be eliminated. Finally, use of TZDs might be limited by the increased incidence of peripheral edema and heart failure. Although incidence of peripheral edema or heart failure did not differ between patients treated with and patients treated without pioglitazone in this study, the long-term impact of pioglitazone on cardiac function and the incidence of heart failure should be carefully monitored.

Conclusions

Pioglitazone suppresses in-stent neointimal proliferation and therefore reduces angiographical and clinical restenosis 6 months after PCI in patients with T2DM. The additive impact of pioglitazone on restenosis and TLR as well as stent thrombosis after placement of DES needs further investigations.

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